Systolic blood pressure reduction during the first 24 h in acute heart failure admission

VERITAS Investigators

Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.889

Publication date:
2018

European Journal of Heart Failure (2018) **20**, 317–322
doi:10.1002/ejhf.889

RESEARCH ARTICLE

Systolic blood pressure reduction during the first 24 h in acute heart failure admission: friend or foe?

Gad Cotter[1]*, Marco Metra[2], Beth A. Davison[1], Guillaume Jondeau[3], John G.F. Cleland[4,5], Robert C. Bourge[6], Olga Milo[1], Christopher M. O'Connor[7], John D. Parker[8], Guillermo Torre-Amione[9], Dirk J. van Veldhuisen[10], Isaac Kobrin[11], Maurizio Rainisio[12], Stefanie Senger[1], Christopher Edwards[1], John J.V. McMurray[13], and John R. Teerlink[14,15], for the VERITAS Investigators

[1]Momentum Research, Inc., Durham, NC, USA; [2]Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [3]Cardiology Service, Bichat Hospital, Paris, France; [4]Department of Cardiology, University of Hull, Kingston upon Hull, UK; [5]National Heart and Lung Institute, Royal Brompton and Harefield Hospitals NHS Trust, Imperial College, London, UK; [6]Department of Medicine, Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, AL, USA; [7]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA; [8]Division of Cardiology, Mount Sinai Hospital, Toronto, ON, Canada; [9]Methodist DeBakey Heart and Vascular Center, Methodist Hospital, Houston, TX, USA; [10]Department of Cardiovascular Disease, University Medical Centre Groningen, Groningen, the Netherlands; [11]Kobrin Associates GmbH, Basel, Switzerland; [12]AbaNovus Srl, Sanremo, Italy; [13]Department of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [14]Department of Medicine, Faculty of Cardiology, University of California San Francisco, San Francisco, CA, USA; and [15]Department of Medicine, San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA

Received 25 January 2017; revised 28 March 2017; accepted 12 April 2017; online publish-ahead-of-print 4 September 2017

Aims Changes in systolic blood pressure (SBP) during an admission for acute heart failure (AHF), especially those leading to hypotension, have been suggested to increase the risk for adverse outcomes.

Methods and results We analysed associations of SBP decrease during the first 24 h from randomization with serum creatinine changes at the last time-point available (72 h), using linear regression, and with 30- and 180-day outcomes, using Cox regression, in 1257 patients in the VERITAS study. After multivariable adjustment for baseline SBP, greater SBP decrease at 24 h from randomization was associated with greater creatinine increase at 72 h and greater risk for 30-day all-cause death, worsening heart failure (HF) or HF readmission. The hazard ratio (HR) for each 1 mmHg decrease in SBP at 24 h for 30-day death, worsening HF or HF rehospitalization was 1.01 [95% confidence interval (CI) 1.00–1.02; $P = 0.021$]. Similarly, the HR for each 1 mmHg decrease in SBP at 24 h for 180-day all-cause mortality was 1.01 (95% CI 1.00–1.03; $P = 0.038$). The associations between SBP decrease and outcomes did not differ by tezosentan treatment group, although tezosentan treatment was associated with a greater SBP decrease at 24 h.

Conclusions In the current post hoc analysis, SBP decrease during the first 24 h was associated with increased renal impairment and adverse outcomes at 30 and 180 days. Caution, with special attention to blood pressure monitoring, should be exercised when vasodilating agents are given to AHF patients.

Keywords Blood pressure • Acute heart failure • Outcome

Introduction

Vasodilating agents are among the recommended first-line therapies in patients admitted for acute heart failure (AHF),[1,2] despite a lack of evidence supporting their efficacy beyond the first hours of admission.[3] A drop in systolic blood pressure (SBP) during the first days of admission has been observed in several studies;[4–6] however, the predictors of SBP decreases and the associations of such

*Corresponding author. Momentum Research, Inc., 3100 Tower Boulevard, Suite 802, Durham, NC 27707, USA. Tel: +1 919 287 1824, Fax: +1 919 287 1825, Email: gadcotter@momentum-research.com

blood pressure (BP) decreases with outcomes were not reported in detail. An analysis of one small study did suggest that SBP reduction may be associated with untoward pathophysiological effects such as worsening of kidney function.[7] Such a potential deleterious effect of an SBP decrease may explain, at least in part, the results of some clinical studies in which pharmacologically induced SBP decreases led to deteriorations in renal function and subsequent adverse outcomes.[8–10] This conclusion was strengthened by a recent analysis of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, which suggested that hypotension is relatively common during AHF hospitalization, and imposes a significant negative prognostic impact on 30-day outcomes.[11] In the current analysis, we assessed predictors of SBP changes at 24 h from study drug initiation (24–48 h from admission) and their associations with worsening kidney function and clinical outcomes in the Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Studies (VERITAS).[4,5]

Methods

The VERITAS project comprised two identical, concurrent randomized trials that evaluated the efficacy of tezosentan administration within 24 h of hospital presentation for AHF.[4,5] Inclusion criteria required patients to have reported dyspnoea at rest after receipt of i.v. diuretics and to have at least two of four objective signs of heart failure (HF): elevated natriuretic peptides; pulmonary oedema on physical examination; pulmonary congestion or oedema on chest X-ray, and left ventricular systolic dysfunction evidenced by reduced ejection fraction or wall motion index. Patients with SBP of ≤100 mmHg, or ≤120 mmHg if receiving a vasodilator, were excluded. Patients enrolled in error more than 24 h after presentation and patients without a measured SBP at 24 h were also excluded from the analyses.

Routine laboratory measurements at baseline, 24 h and 72 h were obtained locally, whereas troponin I and brain natriuretic peptide levels were assayed centrally. Patients were followed for worsening HF for 30 days, and vital status was assessed at 6 months.

Statistical analysis

Summary statistics are reported as the mean and standard deviation for continuous variables, and as the median (interquartile range) for skewed variables; proportions in each category are presented for categorical variables. Patients were grouped by tertiles of the change in SBP from baseline to 24 h and baseline characteristics were compared using analysis of variance (ANOVA) or Cochran–Mantel–Haenszel χ^2 tests, as appropriate.

Linear regression was used to model the associations of baseline characteristics with the change in SBP from baseline to 24 h. Non-linearity of the association between each continuous variable and SBP change was assessed by testing the contribution of the non-linear terms of a restricted cubic spline transformation with four knots. A linear spline, quadratic or cubic polynomial, or log transformation, was chosen, based on the Akaike's information criterion, to model non-linear associations. Ten multiple imputation datasets assuming multivariate normality were used for missing baseline covariates,[12] and parameter estimates were averaged over these imputation datasets using Rubin's algorithm.[13] A multivariable model was selected in each imputation dataset from among the baseline characteristics using backward elimination with a retention criterion of $P < 0.05$; the final model included those covariates included in at least six of the 10 imputation datasets. The unadjusted association of SBP change at 24 h with creatinine change at 72 h was assessed using linear regression. Logistic regression was used to provide the odds ratios for the association between SBP change at 24 h and an increase in creatinine of ≥0.3 mg/dL at 72 h, with covariates for multivariable adjustment selected using the methodology described above.

Associations between the SBP changes and 30-day all-cause death or HF readmission, and 180-day all-cause death, were examined using Cox proportional hazards models. Potential confounding was addressed through multivariable adjustment for baseline SBP and covariates previously found to be prognostic of these outcomes.[14]

SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for all analyses.

Results

Of the 1449 patients randomized, 102 patients were enrolled at more than 24 h from presentation and 90 patients lacked data on the change in SBP at 24 h. These patients were excluded from the dataset, leaving 1257 patients for analysis.

Patients' baseline characteristics by tertiles of SBP change at 24 h are presented in *Table 1*. Unadjusted and multivariable-adjusted associations between baseline characteristics and SBP decrease at 24 h are presented in *Table 2*. Predictors of a larger SBP drop at 24 h were lack of atrial fibrillation or diabetes mellitus, higher baseline SBP, longer QRS interval, higher blood urea nitrogen (BUN), and lower white blood cell count. Respiratory rate, heart rate and creatinine had non-linear relationships with SBP change. Tezosentan treatment was associated with a larger mean SBP decrease at 24 h [mean difference 6.17, 95% confidence interval (CI) 4.39–7.96; $P < 0.001$].

Change in SBP at 24 h was inversely associated with change in creatinine at 72 h (*Figure 1*). The relationship had an inflection point around −15 mmHg; that is, SBP decreases of >15 mmHg were associated with a numerical acceleration in creatinine increase, although the departure from non-linearity was not statistically significant ($P = 0.5910$). The percent is out of subjects in the analysis population with non-missing creatinine change at day 3. 222/1068 (20.8%) had a creatinine change of ≥0.3 mg/dL at 72 h. Patients with larger decreases in SBP at 24 h were more likely to have a creatinine change of ≥0.3 mg/dL at 72 h [odds ratio (OR) per 1 mmHg greater decrease in SBP: 1.01, 95% CI 1.00–1.02; $P = 0.0272$]. The association of SBP change with creatinine increase did not differ significantly by tezosentan treatment (interaction $P = 0.7239$). After multivariable adjustment for factors found to be associated with a creatinine change of ≥0.3 mg/dL at 72 h in the VERITAS database (supplementary material online, *Table S1*) [age, renal impairment, time from admission to randomization, respiratory rate and estimated glomerular filtration rate (eGFR)], the association of SBP change with a creatinine change of ≥0.3 mg/dL was of borderline statistical significance (OR per 1 mmHg decrease in SBP: 1.01, 95% CI 1.00–1.01; $P = 0.0941$). Tezosentan treatment was not significantly associated with the risk for a creatinine increase of ≥0.3 mg/dL, and further adjustment for tezosentan treatment did not affect the association of SBP change with outcome.

Table 1 Baseline characteristics by tertiles of systolic blood pressure (SBP) change to 24 h

	SBP change, mmHg				All subjects ($n = 1257$)
	≤ -19 ($n = 423$)	> -19 to ≤ -3 ($n = 424$)	> -3 ($n = 410$)	*P*-value[a]	
Age, years, mean ± SD	71.0 ± 12.01	69.9 ± 11.93	69.9 ± 12.49	0.3321	70.3 ± 12.14
Gender: male, *n* (%)	238 (56.3%)	263 (62.0%)	241 (58.8%)	0.4522	742 (59.0%)
Race: White, *n* (%)	353 (83.5%)	371 (87.5%)	362 (88.3%)	0.0409	1086 (86.4%)
Time to randomization, h, mean ± SD	10.2 ± 6.64	10.9 ± 7.02	11.4 ± 6.87	0.0423	10.8 ± 6.86
BMI, kg/m^2, mean ± SD	29.2 ± 6.47	28.8 ± 6.01	28.9 ± 6.28	0.7039	28.9 ± 6.25
Treated with tezosentan, *n* (%)	242 (57.2%)	242 (57.1%)	157 (38.3%)	<0.0001	641 (51.0%)
Atrial fibrillation on admission, *n* (%)	96 (22.7%)	112 (26.7%)	118 (29.1%)	0.0364	326 (26.2%)
History of CHF, *n* (%)	299 (70.9%)	325 (77.4%)	291 (71.9%)	0.7249	915 (73.4%)
History of COPD, *n* (%)	74 (17.5%)	84 (19.9%)	74 (18.0%)	0.8303	232 (18.5%)
History of diabetes, *n* (%)	211 (49.9%)	216 (51.1%)	184 (44.9%)	0.1519	611 (48.6%)
History of hyperlipidaemia, *n* (%)	142 (33.6%)	158 (37.4%)	145 (35.4%)	0.5818	445 (35.4%)
History of hypertension, *n* (%)	361 (85.3%)	329 (77.8%)	317 (77.3%)	0.0035	1007 (80.2%)
History of smoking, *n* (%)	28 (6.6%)	31 (7.3%)	37 (9.0%)	0.1926	96 (7.6%)
History of IHD, PVD, stroke, *n* (%)	284 (67.1%)	302 (71.4%)	294 (71.7%)	0.1484	880 (70.1%)
History of mitral/aortic valve disease, *n* (%)	75 (17.7%)	63 (14.9%)	65 (15.9%)	0.4573	203 (16.2%)
History of renal impairment, *n* (%)	161 (38.2%)	166 (39.6%)	138 (34.1%)	0.2312	465 (37.3%)
History of liver disease, *n* (%)	30 (7.1%)	36 (8.6%)	31 (7.7%)	0.7631	97 (7.8%)
Previous PCI or CABG, *n* (%)	136 (32.2%)	159 (37.6%)	150 (36.6%)	0.1779	445 (35.4%)
On i.v. nitrates at randomization, *n* (%)	73 (17.3%)	65 (15.3%)	69 (16.8%)	0.8622	207 (16.5%)
Furosemide i.v. over 24 h, mg, median (IQR)	40.0 (0.0–120.0)	40.0 (0.0–120.0)	40.0 (0.0–120.0)	0.6385	40.0 (0.0–120.0)
ACE inhibitors, *n* (%)	224 (53.0%)	236 (55.7%)	204 (49.8%)	0.3622	664 (52.8%)
Beta-blockers, *n* (%)	201 (47.5%)	216 (50.9%)	176 (42.9%)	0.1905	593 (47.2%)
Angiotensin inhibitors, *n* (%)	55 (13.0%)	41 (9.7%)	35 (8.5%)	0.0345	131 (10.4%)
Calcium channel blockers, *n* (%)	78 (18.4%)	42 (9.9%)	63 (15.4%)	0.1980	183 (14.6%)
Oral loop diuretics, *n* (%)	136 (32.2%)	121 (28.5%)	115 (28.0%)	0.1931	372 (29.6%)
SBP, mmHg, mean ± SD	147.3 ± 23.11	126.8 ± 17.82	121.9 ± 16.84	<0.0001	132.1 ± 22.37
Respiratory rate, breaths/min, mean ± SD	26.5 ± 4.43	26.0 ± 3.87	26.2 ± 4.22	0.1661	26.2 ± 4.18
Heart rate, b.p.m., mean ± SD	84.4 ± 16.97	83.6 ± 18.16	83.2 ± 17.78	0.5998	83.7 ± 17.63
ECG QRS interval, ms, mean ± SD	113.4 ± 35.40	114.2 ± 36.22	112.0 ± 34.82	0.6713	113.2 ± 35.48
Baseline dyspnoea VAS, mm, mean ± SD	62.8 ± 23.57	63.2 ± 23.12	61.9 ± 23.06	0.7096	62.6 ± 23.24
Albumin, g/L, mean ± SD	38.0 ± 5.01	37.4 ± 5.27	37.8 ± 5.18	0.3683	37.7 ± 5.16
ALT, U/L, median (IQR)	18.2 (12.0–29.0)	18.6 (12.7–30.0)	18.7 (12.7–28.1)	0.4938	18.6 (12.6–29.1)
BUN, mmol/L, median (IQR)	8.2 (6.0–11.2)	8.3 (6.4–11.2)	7.9 (6.2–11.0)	0.0204	8.2 (6.2–11.1)
Creatinine, umol/L, mean ± SD	115.7 ± 40.08	118.7 ± 36.82	116.1 ± 39.16	0.4711	116.8 ± 38.70
Haemoglobin, g/dL, mean ± SD	13.4 ± 1.88	13.3 ± 1.84	13.4 ± 1.94	0.9834	13.3 ± 1.88
Sodium, mmol/L, mean ± SD	139.1 ± 3.92	138.6 ± 4.06	138.6 ± 4.03	0.1231	138.7 ± 4.01
WBC count, $\times 10^9$/L, mean ± SD	9.7 ± 3.58	9.5 ± 3.70	10.2 ± 4.18	0.0162	9.8 ± 3.84
BNP, pg/mL, median (IQR)	437.0 (153.0–949.0)	419.0 (153.0–968.0)	404.0 (152.0–903.0)	0.6709	416.0 (153.0–936.0)
Troponin I, ng/mL, median (IQR)	0.0400 (0.0005–0.1260)	0.0350 (0.0005–0.1290)	0.0340 (0.0005–0.1285)	0.5221	0.0360 (0.0005–0.1275)

ALT, alanine aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; IHD, ischaemic heart disease; IQR, interquartile range; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation; VAS, visual analogue scale; WBC, white blood cell (leucocyte).
[a]*P*-value according to Cochran–Mantel–Haenszel χ^2 test for categorical variables and *F*-test for continuous variables.

Table 2 Univariable and multivariable associations of baseline characteristics with characteristics by tertiles of systolic blood pressure (SBP) decrease at 24 h

Predictor		Univariable models		Multivariable models	
	Estimate for change of:	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value
Age	10	0.23 (−0.67 to 1.12)	0.623		
Gender: male	Yes vs. no	−2.13 (−4.34 to 0.09)	0.060		
Race: White	Yes vs. no	−3.13 (−6.31 to 0.04)	0.053		
Time to randomization, h	1	−0.24 (−0.40 to −0.08)	0.003		
BMI, kg/m^2	1	0.06 (−0.12 to 0.24)	0.497		
Atrial fibrillation on admission	Yes vs. no	−4.40 (−6.87 to −1.92)	<0.001	−3.34 (−5.43 to −1.26)	0.002
History of CHF	Yes vs. no	−0.74 (−3.21 to 1.74)	0.561		
History of COPD	Yes vs. no	−0.67 (−3.48 to 2.14)	0.642		
History of diabetes	Yes vs. no	0.80 (−1.38 to 2.99)	0.470	−2.22 (−4.04 to −0.40)	0.017
History of hyperlipidaemia	Yes vs. no	−0.49 (−2.77 to 1.79)	0.675		
History of hypertension	Yes vs. no	4.00 (1.28–6.72)	0.004		
History of smoking	Yes vs. no	−1.60 (−5.70 to 2.51)	0.446		
History of IHD, PVD, stroke	Yes vs. no	−0.73 (−3.11 to 1.65)	0.550		
History of mitral/aortic valve disease	Yes vs. no	0.75 (−2.21 to 3.71)	0.618		
History of renal impairment	Yes vs. no	0.39 (−1.87 to 2.66)	0.732		
History of liver disease	Yes vs. no	0.23 (−3.85 to 4.31)	0.912		
Previous PCI or CABG	Yes vs. no	−1.98 (−4.26 to 0.30)	0.089		
On i.v. nitrates at randomization	Yes vs. no	−0.12 (−3.06 to 2.82)	0.936		
Furosemide i.v. over 24 h, mg	5	−0.01 (−0.05 to 0.04)	0.810		
Systolic blood pressure, mmHg	1	0.47 (0.43–0.51)	<0.001	0.49 (0.45–0.53)	<0.001
Respiratory rate ≤24 breaths/min	5	−0.40 (−4.35 to 3.56)	0.036		
Respiratory rate >24 breaths/min	5	2.03 (0.46–3.59)			
Heart rate, b.p.m.[a]	94.50 vs. 82.00	0.35 (−0.42 to 1.13)	0.357	1.33 (0.67–1.99)	<0.001
	82.00 vs. 71.00	0.90 (−0.05 to 1.85)		1.77 (0.98–2.57)	
ECG QRS interval, ms	1	0.00 (−0.03 to 0.04)	0.777	0.05 (0.03–0.08)	<0.001
Dyspnoea VAS	1	0.02 (−0.03 to 0.06)	0.478		
Albumin, g/L	1	0.09 (−0.15 to 0.32)	0.469		
ALT, U/l	Doubling	−0.80 (−1.93 to 0.34)	0.169		
BUN, mmol/L	Doubling	0.38 (−1.21 to 1.96)	0.642	1.53 (0.18–2.87)	0.026
Creatinine ≤120 μmol/L	5	−0.32 (−0.65 to 0.01)	0.099		
Creatinine >120 μmol/L	5	0.22 (−0.02 to 0.46)			
Haemoglobin, g/dL	1	−0.00 (−0.58 to 0.58)	0.992		
Sodium, mmol/L	3	0.67 (−0.15 to 1.49)	0.112		
WBC count, ×10^9/L	1	−0.27 (−0.56 to 0.01)	0.060	−0.33 (−0.56 to −0.09)	0.006
BNP, pg/mL	Doubling	0.29 (−0.28 to 0.86)	0.314		
Troponin I, ng/mL	Doubling	−0.03 (−0.30 to 0.24)	0.848		
Treated with tezosetan	Yes vs. no	6.85 (4.71 to 9.00)	<0.001	6.17 (4.39–7.96)	<0.001

BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CHF, chronic heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; WBC, white blood cell (leucocyte).
[a]Non-linear association modelled as quadratic transformation. Estimates for the 75th percentile vs. the median, and for the median vs. the 25th percentile are presented.

Similarly, SBP decrease at 24 h was associated with a greater risk for adverse outcomes at both 30 days and 180 days. All-cause death, worsening HF or HF readmission within 30 days occurred in 395 of 1257 (31.4%) patients and 165 of 1257 (13.1%) patients died within 180 days. After multivariable adjustment, the hazard ratio (HR) for each 1 mmHg decrease in SBP at 24 h for 30-day death, worsening HF or HF rehospitalization was 1.01 (95% CI 1.00–1.02; $P = 0.021$), and this association did not differ by randomized treatment (interaction $P = 0.3409$). A larger decrease at 24 h in SBP was also associated with an increased risk for all-cause mortality at 180 days. For 30-day death, worsening HF or HF readmission, covariates for multivariable adjustment were age, heart rate, respiratory rate, history of chronic HF, history of diabetes, history of chronic obstructive pulmonary disease (COPD), SBP, renal impairment, baseline score for dyspnoea on a visual analogue scale (VAS), albumin, BUN, haemoglobin and sodium.[14] For 180-day all-cause death, covariates for multivariable adjustment were age, heart rate, history of ischaemic heart disease, peripheral vascular disease or stroke, SBP, baseline dyspnoea VAS, history of COPD, albumin, BUN, white blood cell count and sodium.[14] After multivariable adjustment, the HR for each 1 mmHg decrease in SBP at 24 h for 180-day all-cause mortality was 1.01 (95% CI 1.00–1.03; $P = 0.038$). There was no interaction between SBP decrease and outcomes in tezosentan-treated vs.

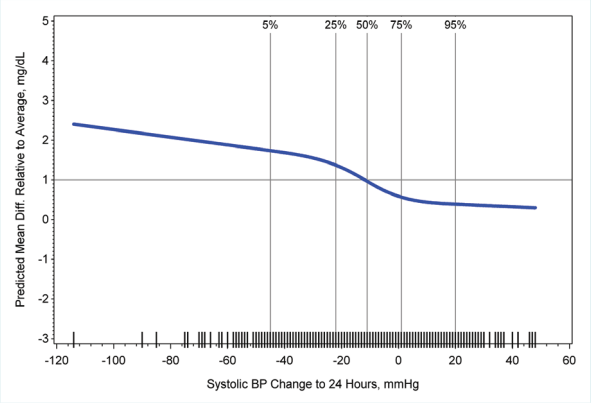

Figure 1 Association of systolic blood pressure (SBP) change at 24 h with creatinine change at 72 h. The predicted value of the change in creatinine relative to the average change is plotted as a restricted cubic spline function of SBP change with knots at −45, −18, −4 and 20 mmHg. Vertical tick marks represent individual patient values of SBP change. Vertical reference lines for the 5th, 25th, 50th, 75th and 95th percentiles of the SBP change distribution are shown.

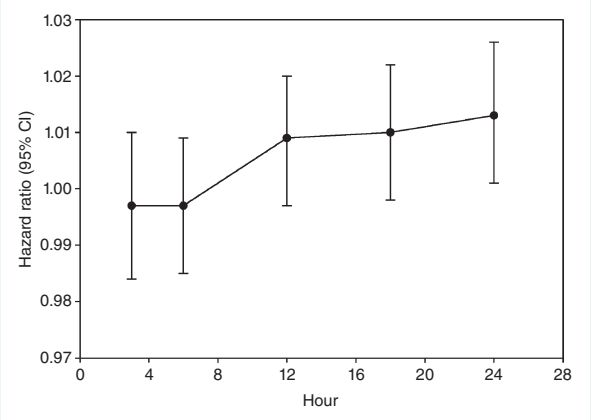

Figure 2 Association of systolic blood pressure (SBP) decrease by time from randomization with 180-day all-cause death, showing the hazard ratio per 1 mmHg greater decrease in SBP with associated 95% confidence intervals (CIs).

placebo-treated patients (interaction $P = 0.1414$). *Figure 2* depicts the association between 180-day mortality and SBP decrease at different time-points to 24 h and suggests a lack of significance in the first 12 h and an increased effect of SBP decrease with time.

Discussion

The present analysis of VERITAS data suggests an inverse correlation between SBP changes and renal function as measured by creatinine changes at 72 h, as well as 30- and 180-day outcomes in patients with AHF. Patients with larger decreases in BP were especially prone to creatinine increases, as well as increased risk for 30-day death, worsening HF or HF readmission, and 180-day mortality.

The results of these analyses are largely in line with those of previous studies, and both confirm and supplement them. In a small analysis of the Pre-RELAX-AHF (Relaxin in Acute Heart Failure) Phase 2 study, Voors *et al.*[7] showed that BP decrease is associated with renal function deterioration. An analysis of the larger ASCEND-HF study[11] demonstrated that hypotension, strictly defined as an SBP decrease to <90 mmHg regardless of initial BP, was associated with increased risk for adverse outcome at 30 days, but not with renal impairment at day 10 or discharge. As the restrictions imposed by the selection of the subgroup analysed in ASCEND-HF (i.e. patients with hypotension defined by a specific cut-off and assessment of renal function distant from the event) limit the analysis to a specific subgroup of patients, it is possible that a relative decrease in SBP rather than the reaching of an arbitrary threshold is more important prognostically. Indeed, in the present analysis, baseline-adjusted SBP decreases were associated both with more adverse outcomes and with more renal impairment, regardless of the magnitude of decrease in SBP.

The relationship between SBP changes and outcomes after treatment with vasodilating agents has not been thoroughly studied in the past. In the current analysis, no interaction was found between SBP decrease, drug therapy and outcomes ($P = 0.1414$ for 180-day mortality), although, as noted previously, active therapy with tezosentan was associated with a greater decrease in SBP. Thus, the increased risk associated with a larger drop in SBP may have neutralized the beneficial effects of the new treatment.

Previous studies have suggested that such SBP lowering induced by active interventions may lead to more adverse outcomes. In earlier studies, in which doses of nesiritide higher than those given in ASCEND-HF were administered, nesiritide therapy led to more hypotension, renal impairment and increased mortality.[9] However, this finding was not replicated in the ASCEND-HF study, in which lower doses of nesiritide were administered. In the REVIVE study, similar findings were reported and greater hypotension in the active arm was associated with a trend towards earlier mortality,[8] especially in patients enrolled with lower BP at screening. Finally, in the recently reported TRUE-AHF study, administration of ularitide was associated with a greater SBP decrease in the active arm (approximately 10 mmHg at 24 h), an increase in creatinine and a numerical increase in early mortality at 180–240 days.[10] These results can be explained by some negative effects of BP decreases on perfusion in end organs such as kidneys,[7] although data on the mechanism behind why such decreases in BP may be detrimental are not available. These findings may underestimate the true negative effects of BP reduction in AHF as creatinine is not a perfect measure of kidney dysfunction.[15] Further, no studies examining the effects of agents with vasodilating effects have ever demonstrated beneficial effects in patients with AHF beyond the first few hours of admission. Most importantly, the effects of administration of i.v. nitrates beyond the first 1–2 h of admission have never been examined in detail, although these agents are recommended in guidelines for the treatment of AHF.[1] Interestingly, the present data also show that early changes in SBP have no relationship

with outcomes, whereas changes that occur beyond 12 h from admission are associated with worse outcomes. Hence, the totality of the evidence – in both the current and previous analyses, as well as prospective studies – begs the question of whether vasodilation, long held as a pillar of therapy for AHF, does indeed benefit patients beyond the first hours of administration, especially once normal SBP values are reached. These data would suggest that our knowledge of the effects of vasodilation in AHF is incomplete and studies to examine such effects may be urgently needed. In the meantime, physicians should exercise caution when administering vasodilating agents to patients with AHF, especially when they cause a significant reduction in SBP of >15–25 mmHg or when a low SBP is reached.

Limitations

The current analysis is a post hoc analysis of data from the VERITAS project and as such should be seen as hypothesis-generating and not as definitive.

Conclusions

Systolic blood pressure decreases in patients with AHF are associated with more early renal impairment and an increase in adverse outcomes at 30 and 180 days. Studies examining the effects of vasodilating agents such as i.v. nitrates in AHF are urgently needed and, until such studies are performed, caution should be exercised in the administration of these agents to patients with AHF, especially when significant falls in SBP are observed.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Multivariable associations of baseline characteristics with creatinine change of ≥0.3 mg/dL at 72 h.

Conflict of interest: G.C., B.A.D., O.M., S.S. and C.E. are employees of Momentum Research, which has provided consulting services to NovaCardia, Merck, Corthera, Novartis, Singulex, ChanRx, Laguna Pharmaceuticals, Sorbent Therapeutics, Celyad SA, Trevena, Amgen and Anexon. M.M. has received consulting honoraria from Bayer, Novartis and Servier. G.J. has received consulting fees from Novartis and ResMed. J.G.F.C. has received research funding and personal honoraria from Actelion, Amgen, Novartis and Trevena. I.K. served as a head of clinical development in Actelion during the VERITAS trials. J.R.T. has received research grants or consulting fees from Actelion, Amgen, Bayer, Cytokinetics, Novartis and Trevena. The other authors report no conflicts.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
2. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, Ristic AD, Lambrinou E, Masip J, Riley JP, McDonagh T, Mueller C, deFilippi C, Harjola VP, Thiele H, Piepoli MF, Metra M, Maggioni A, McMurray J, Dickstein K, Damman K, Seferovic PM, Ruschitzka F, Leite-Moreira AF, Bellou A, Anker SD, Filippatos G. Recommendations on pre-hospital and early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail* 2015;**17**:544–558.
3. Cotter G, Davison B. Intravenous therapies in acute heart failure – lack of effect or lack of well powered studies? *Eur J Heart Fail* 2014;**16**:355–357.
4. Teerlink JR, McMurray JJ, Bourge RC, Cleland JG, Cotter G, Jondeau G, Krum H, Metra M, O'Connor CM, Parker JD, Torre-Amione G, van Veldhuisen DJ, Frey A, Rainisio M, Kobrin I; VERITAS Investigators. Tezosentan in patients with acute heart failure: design of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Study (VERITAS). *Am Heart J* 2005;**150**:46–53.
5. McMurray JJ, Teerlink JR, Cotter G, Bourge RC, Cleland JG, Jondeau G, Krum H, Metra M, O'Connor CM, Parker JD, Torre-Amione G, van Veldhuisen DJ, Lewsey J, Frey A, Rainisio M, Kobrin I; VERITAS Investigators. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA* 2007;**298**:2009–2019.
6. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF Jr, Dorobantu MI, Grinfeld LR, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin TM, Metra M; RELAXin in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet* 2013;**381**:29–39.
7. Voors AA, Davison BA, Felker GM, Ponikowski P, Unemori E, Cotter G, Teerlink JR, Greenberg BH, Filippatos G, Teichman SL, Metra M; Pre-RELAX-AHF Study Group. Early drop in systolic blood pressure and worsening renal function in acute heart failure: renal results of Pre-RELAX-AHF. *Eur J Heart Fail* 2011;**13**:961–967.
8. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, Padley RJ, Thakkar R, Delgado-Herrera L, Salon J, Garratt C, Huang B, Sarapohja T; REVIVE Heart Failure Study Group. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC Heart Fail* 2013;**1**:103–111.
9. Aaronson KD, Sackner-Bernstein J. Risk of death associated with nesiritide in patients with acutely decompensated heart failure. *JAMA* 2006;**296**:1465–1466.
10. Packer M, O'Connor C, McMurray JJ, Wittes J, Abraham WT, Anker SD, Dickstein K, Filippatos G, Holcomb R, Krum H, Maggioni AP, Mebazaa A, Peacock WF, Petrie MC, Ponikowski P, Ruschitzka F, van Veldhuisen DJ, Kowarski LS, Schactman M, Holzmeister J; TRUE-AHF Investigators. Effect of ularitide on cardiovascular mortality in acute heart failure. *N Engl J Med* 2017;**376**:1956–1964.
11. Patel PA, Heizer G, O'Connor CM, Schulte PJ, Dickstein K, Ezekowitz JA, Armstrong PW, Hasselblad V, Mills RM, McMurray JJ, Starling RC, Tang WH, Califf RM, Hernandez AF. Hypotension during hospitalization for acute heart failure is independently associated with 30-day mortality: findings from ASCEND-HF. *Circ Heart Fail* 2014;**7**:918–925.
12. Schafer JL. *Analysis of Incomplete Multivariate Data*. New York, NY: Chapman & Hall; 1997.
13. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley & Sons; 1987.
14. Cleland JG, Teerlink JR, Davison BA, Shoaib A, Metra M, Senger S, Milo O, Cotter G, Bourge RC, Parker JD, Jondeau G, Krum H, O'Connor CM, Torre-Amione G, van Veldhuisen DJ, McMurray JJ; VERITAS Investigators. Measurement of troponin and natriuretic peptides shortly after admission in patients with heart failure-does it add useful prognostic information? An analysis of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Studies (VERITAS). *Eur J Heart Fail* 2017;**19**:739–747.
15. van Veldhuisen DJ, Ruilope LM, Maisel AS, Damman K. Biomarkers of renal injury and function: diagnostic, prognostic and therapeutic implications in heart failure. *Eur Heart J* 2016;**37**:2577–2585.